REMARKS

Entry of the present amendment and reconsideration of the above-referenced application is respectfully requested. Claims 1-29 and 31-39 are pending, claims 37-39 having been added by way of the present amendment. Claims 1-14 and 27 have been withdrawn from consideration. Claims 15, 26, 28, and 29 are in independent form.

CLAIMS 26 AND 29

Independent claims 26 and 29 stand rejected under 35 U.S.C. § 103(a) as obvious over the publication of Uo et al. (J. Ceram. Soc. Jpn. Vol. 100, p. 426-429, hereinafter "Uo") and U.S. Patent No. 4,148,689 to Hino et al. (hereinafter "Hino").

Applicants respectfully traverse the rejection.

Claim 26 relates to a method that includes mixing a vegetative cell into a sol, mixing a sufficient amount of a dispersant into said sol to cause macropores in a gel formed by the sol; and gelling the sol to form the gel. Claim 29 relates to a gel that includes a solid network formed by the condensation of hydroxy metallates from a sol solution and a vegetative cell added to the sol solution and thereby immobilized within said solid network. The solid network defines macropores.

In rejecting claims 26 and 29, it is asserted that it would have been obvious to use the vegetative cells described by Hino in place of the yeast spores of Uo. Applicants respectfully disagree with this assertion and traverse the rejection. In particular, it is submitted that there is no reason to believe that one of ordinary skill would be motivated to combine the references in the manner suggested with a reasonable expectation of success.

To begin with, this assertion neglects the express teachings of Uo regarding the need for robust immobilants. Uo expressly teaches that yeast spores, rather than yeast or other vegetative cells, are to be immobilized due to their durability to organic solvents. See Uo, Section 2.2, page 427.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the appellant." In re Gurley, 27 F.3d 551 (Fed. Cir. 1994). The totality of a reference's teachings must be considered when determining if a reference teaches away. W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1550-51 (Fed.Cir.1983), cert. denied, 469 U.S. 851 (1984). "As a

'useful general rule,' ... references that teach away cannot serve to create a prima facie case of obviousness." McGinley v. Franklin Sports, Inc., 262 F.3d 1339 (Fed. Cir. 2001).

The rejection has never indicated why this general rule is to be ignored in this case. The express language in Uo clearly states that the durability of yeast spores is a requirement for immobilization in Uo's matrices. To pretend otherwise is to engage in hindsight-based reconstruction of applicants' invention, without due consideration of the express teachings of Uo as a whole. As such, there is no reasonable expectation of success and a *prima facie* case of obviousness has not been established.

In further support of this, the assertion that it would have been obvious to use the vegetative cells described by Hino in the matrices of Uo also ignores the well-known antimicrobial properties of alcohols. Alcohols, such as the methanol present in the sol solutions of Uo, have long been recognized as effective antimicrobial agents. See, e.g., Chapter 12 of the 5th Edition of *Disinfection, Sterilization, and Preservation* edited by Seymour Block[1] (submitted with the Response filed July 25, 2003), which discusses the antimicrobial properties of alcohols in general, and methanol in particular, toward, e.g., both vegetative bacteria[2] and bacterial spores.[3] Assuming that the spore suspensions of Uo are entirely water and that the tetramethylorthosilicate (TMOS) in the starting solution completely prehydrolyzes,[4] Uo's gelation solutions are approximately 45-55 vol.% methanol.[5] The yeast spores in Uo are exposed to these solutions for over one day. Attention is respectfully directed to table 12.4 on page 235 of Block which describes that 65 vol.% methanol is microbicidal to both *Staphylococcus aureus* and *Escherichia coli* in under one minute in suspension tests, and that 9 vol.% methanol is effective at inhibiting *S. aureus* growth. Attention is further directed to table 12.7 on page 236 of

[1] Lippincott Williams & Wilkins, Philadelphia, PA, U.S.A. (2001).
[2] Page 234-238 of Block.
[3] Page 238-239 of Block.
[4] Uo et al. prehydrolyze starting solutions for 1 day at 20°C in sealed containers. See, e.g., section 2.3 of Uo et al.
[5] Attention is respectfully directed to Table 3 of Uo et al. which lists the compositions of starting solutions for the immobilization of yeast spores. If one assumes that the spore suspension is entirely water, then Composition A includes approximately 17 moles of water, and Composition B includes approximately 11 moles of water. After complete hydrolysis of the TMOS in the starting solution, Compositions A and B each include approximately 6 moles of methanol (2 moles added and 4 moles released by hydrolysis of 1 mole of TMOS). The methanol/water molar ratios of Compositions A and B before spore addition are approximately 6:17 and 6:11, respectively. Methanol has a gram molecular weight of 32.04 g/mol and a density of 0.791 g/mL. Water has a gram molecular weight of 18.02 g/mol and a density of 1.0 g/mL. Neglecting volume contraction, Compositions A and B each include approximately 243 mL of methanol, Composition A includes approximately 298 mL of water, and Composition B includes approximately 193 mL of water.

Block which illustrates that germicidal activity can be achieved with decreased concentrations of ethanol when exposure time is increased.

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, *viewed in the light of the prior art.*" In re Dow Chemical Co., 837 F.2d 469, 473 (Fed. Cir. 1988) (emphasis added). "In determining whether such a suggestion can fairly be gleaned from the prior art, the *full field of the invention must be considered*; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *Id.* (emphasis added). "The PTO *must also give weight* to objective evidence of non-obviousness during patent prosecution." In re Sernaker, 702 F.2d 989, 996 (Fed.Cir.1983) (emphasis added).

It is respectfully submitted that, in the present case, the technological literature itself indicates that there is no reasonable expectation of success with the proposed combination. Moreover, the rejection does not give the technological literature its due weight, nor presented any grounds for ignoring the express teachings thereof. It is therefore respectfully submitted that a *prima facie* case of obviousness has not been established.

Additional evidence suggestive of the contention that one of ordinary skill would not be motivated to combine the references in that manner suggested can also be found in the other cited reference, namely Hino. In particular, Hino describes that sols containing cells can be extrusion cast into organic solvents. See col. 20, lines 44-45 and col. 9, line 14-22 of Hino. In the example of extrusion casting detailed by Hino, the gels were freeze-dried immediately after extrusion and the relative activity of *Erwinia herbicola* after casting in isopropyl alcohol was approximately 61% of the control activity, whereas activities of 84-90% of control were obtained without casting. See, e.g., Tables 6 and 7, and col. 14, line 54-col. 16, line 22. It appears that the immediate freeze drying represents an attempt to minimize exposure of *E. herbicola* to isopropyl alcohol (due to microbicidal activity of isopropyl alcohol described, e.g., in tables 12.4 and 12.5 on page 235 of Block), and that even this attempt was only partially successful since a decrease in activity relative to uncast gels was nevertheless observed. In conclusion, Hino provides further empirical evidence consistent with the microbicidal activity of alcohols and leading away from the proposed combination.

In summary, with one reference expressly teaching away from the proposed combination, the second reference leading away from the proposed combination, and the weight of the technological literature indicates that there is no reasonable expectation of success, it is respectfully submitted that a *prima facie* case of obviousness has not been established and that claims 26 and 29, and the claims dependent therefrom, are patentable under 35 U.S.C. § 103(a).

Although *the rejection has never proposed any grounds that would lead one of ordinary skill to the combination of Uo and Hino with a reasonable expectation of success*, the Office action mailed January 14, 2004 raises additional contentions that the Examiner feels bear on the issue of patentability. For the sake of completeness, applicants now respond to these contentions.

The first such contention is that Hino teaches the production of gels containing macropores. This contention is based on the syllogisms that 1) since Hino's gels contain water soluble polymers and since water soluble polymers can be used to cause macropores, that Hino's gels have macropores, and 2) since Hino uses his gels in a flow-through column, the reaction mixture must be flowing through macropores in Hino's gels. Applicants respectfully disagree with both contentions and further submits that a close reading of Hino provides further evidence of the non-obviousness of the present claims.

In regards to the contention that any amount of water soluble polymer in any gelation solution inherently leads to macropores, attention is respectfully directed to Hino, which *explicitly teaches that gels without macropores are formed in the mere presence of water-soluble polymers.* Rather than being macropores, the pores in the overwhelming majority of Hino's gels are so small that the gels are transparent or the color of immobilized cells. Transparent and colored gels do not scatter or reflect visible wavelength (approx. 400 nm to approx. 700 nm) light. Since these gels do not scatter or reflect visible wavelength light, their *pores are inherently smaller than macropores*. See, e.g., Hino, col. 10, line 20-21 ("a colorless, transparent homogeneous complex lyogel was formed" from a solution containing 50 g of 10% PVA), col. 10, line 25-26 ("complex lyogel [formed from a solution containing 50 g of 10% PVA] ... also was transparent"), col. 10, line 45-46 ("appearance of resulting lyogel [from solution containing 50 g of 10% PVA] were almost the same"), col. 10, line 55-57 ("lyogel was again formed [from a solution containing 50 g of 10% PVA] and was found to have similar appearance (i.e. was colorless and transparent)").

In Hino, *every gel that includes a cell is the color of the immobilized cells* and hence does not scatter visible wavelength light. See, e.g., Hino, col. 13, line 4-5 ("[a] yellowish brown film containing the yeast cells was obtained" from a solution containing 100 Parts of 10% PVA), col. 13, line 45-48 ("gel [from a solution containing 100 Parts of 10% PVA] was spread on a plate and dried by ventilation to obtain a yellowish brown film containing yeast cells"), col. 14, line 13-16 ("The gel, thus obtained [from a solution containing 100 Parts of 10% PVA], was spread on a plate and dried by ventilation at room temperature to obtain a yellowish brown film containing 1 g of yeast cells."). The pores in the gels with immobilized cells are thus smaller than macropores. Indeed, it is respectfully submitted that one of ordinary skill would conclude that Hino appears incapable of making macroporous gels that include biological materials.

There are two gels in Hino that are not completely transparent or the color of immobilized cells and hence not explicitly excluded from including macropores. The first such gel is described at col. 12, line 6 of Hino as a "whitely turbid xerogel." This xerogel does not include a biological material. Moreover, this xerogel had been ventilation dried. Such drying both destroys the lyogel pore structure due to capillary forces and makes the xerogel more inhospital to biological materials.

The second such gel is described at col. 12, line 35 of Hino as a "semi-transparent complex lyogel." This lyogel does not include a biological material and there is no indication in Hino that such a gel can be formed to include a biological material. Moreover, it is respectfully submitted that given the pore sizes of Hino's other gels, this lyogel is most likely to scatter visible light only at the shorter wavelength end of the visible light spectrum and hence not include macropores.

In regards to the contention that since Hino uses his gels in a flow-through column, his gels must include macropores, attention is respectfully directed to Hino which describes that the *gels must be molded after gelation* to be converted into desired shapes. The desired shapes can be "granular-type having a round section and in particularly may be spheres, granules, pellets, filaments and so on." Such molding provides a "desirable flow rate of the reaction mixture through the column reactor." See Hino, col. 8, line 34 – col. 9, line 13.

Applicants respectfully submit that, since Hino's gels are molded into shapes that do not fill the entire volume of a column, the reaction mixture can flow through the interstices between

the shapes rather than through the gels. As such, flow through Hino's column is irrelevant to determining whether or not Hino's gels include macropores.

Another contention that is irrelevant as to whether one of ordinary skill would combine Uo and Hino with a reasonable expectation of success but yet bears response is the contention that Hino suggests that an organic solvent can be omitted when forming gels as described in Uo. It is respectfully submitted that Hino suggests nothing of the sort. Hino's gels are not like Uo's in that *Hino describes that his gels, when they include biological materials, do not include macropores*. There is simply no basis anywhere in Hino for concluding that an organic solvent can be omitted when forming a macroporus gel as described in Uo.

Indeed, every reference of record teaches the exact opposite conclusion—namely that macroporous gels like those in Uo require toxic conditions. As discussed above, Uo was hindered by the toxic conditions required to form macroporous gels. United States Patent 4,148,689 to Nakanishi et al. (cited in the action mailed October 15, 2002) requires thermolysis with urea (or, e.g., formamides and acetamides) at temperatures between 60°C and 200°C and pH's between 9.0 and 11.0 to dissolve the walls of porous inorganic gels. Kajihara et al. in J. Am. Ceram. Soc. 81, p. 2670-2676 (also cited in the action mailed October 15, 2002) describes the macroporous titania gels formed by gelation in a sol solution that contains between five and ten moles of ethanol for every mole water. Every reference of record describes toxic conditions during the formation of macroporous gels.

"In determining whether such a suggestion [to combine references] can fairly be gleaned from the prior art, *the full field of the invention must be considered*; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." In re Dow Chemical Co., 837 F.2d 469, 473 (Fed. Cir. 1988) (emphasis added). Applicants therefore respectfully submit that any assertion that the combination of Uo and Hino is obvious must consider the express teachings of record that lead away from the claimed invention, including the teachings of Uo, Nakanishi et al., and Kajihara et al.

Applicants respectfully submit that applicants are entitled to claims as broad as the prior art and applicants' disclosure will allow. In re Rasmussen, 650 F.2d 1212, 1214 (Cust. & Pat.App. 1981). Here, both cited references, a common understanding of the microbicidal properties of alcohols, and every other reference of record teach or lead away from the claims.

Applicants therefore respectfully submit that claims 26 and 29, along with the claims dependent therefrom, are patentable.

CLAIM 28

Independent claim 28 stands rejected under 35 U.S.C. §103(a) as obvious over Uo and Hino.

Applicants respectfully traverse the rejection.

Claim 28 relates to a gel that includes a macroporous solid network and a bacterial cell. The rejection of claim 28 contends that it would have been obvious to replace the yeast spores in the macroporous solid network of Uo with bacterial spores. *The rejection admits that neither Uo nor Hino deal with bacterial spores.*

Applicants therefore respectfully submit that a *prima facie* case of obviousness of claim 28 has not been established. In short, *every* claim element and limitation must be found in the combined references for the Office to carry its burden of proof, and the rejection over Uo and Hino cannot be maintained. Applicants therefore respectfully submit that claim 28 is patentable over the cited art.

CLAIM 15

Independent claim 15 stands rejected under 35 U.S.C. §103(a) as obvious over Uo, Hino, Klein et al. (Better Ceramics Through Chemistry: MRS Symp. Proc. Vol. 32, p. 33-39) (hereinafter "Klein"), and Rao et al. (J. Sol-Gel Sci. Tech. 3, p. 205-217) (hereinafter "Rao").

Applicants respectfully traverse the rejection.

Claim 15 relates to a sol that includes P moles of a hydroxy metallate, W moles of water, a sufficient amount of a dispersant to cause macropores in a gel formed by said sol, and a biological material. The ratio of W:P is greater than 25:1.

None of Uo, Hino, or Rao describe sol solutions with a water to hydroxy metallate ratio greater than 25:1.

Klein describes a sol solution with a water to hydroxy metallate ratio of 32:1. As discussed in the response filed July 25, 2003, the sol solutions in Klein that have elevated water to hydroxy metallate ratios also have additional ethanol to permit solubility of the increased water in the sol solution. With reference to Block, similar ethanol concentrations result in

alcohol-induced protein coagulation, plasma membrane lysis, the killing of bacterial species, sporicidal activity, viricidal activity, and germicidal activity.

The rejection contends that one of ordinary skill in the art would find a suggestion to combine Uo, Hino, Rao, and Klein based on an increased rate of hydrolysis with a higher amount of water despite the results described in Block. Neglecting the issue as to whether an increased rate of hydrolysis is relevant at all to the immobilization of biological materials, applicants respectfully submit that the suggestion to combine must be accompanied by a reasonable expectation of success. There has never been an identification as to why one of ordinary skill would reasonably expect success with the proposed combination. As discussed in the response filed July 25, 2003, Uo's solutions are approximately 45-55 Vol.% methanol whereas Klein's solutions are approximately 65 Vol.% ethanol and moreover are heated to 80°C. The rejection contends that starting with Uo's already-toxic sol solution and increasing the concentration of the organic solvent, increasing the toxicity of the organic solvent, and increasing the temperature of the sol solution would reasonably be suggested to one of ordinary skill.

Since there is no reasonable expectation of success with the proposed combination, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Applicants therefore respectfully submit that claim 15, and the claims dependent therefrom, are patentable over the cited art.

In view of the above remarks, all of the claims should be in condition for allowance. A formal notice to that effect is respectfully solicited. A check in the amount of $27 for excess claims fees is included.

Respectfully submitted,

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